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THE TERATOGENIC EFFECTS OF THE FUEL JP-10 ON THE ICR MICE.

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JP-10 is a synthesized fuel for Cruise Missiles. It is the exoisomer of 4, 7-methano -1H-indene, octahydro 12 aα, 4α, 7α, 7aα (CA #2825-83-4). Pregnant ICR mice were given oral doses of 0.2, 0.4, 0.6 and 0.8 ml/kg on days 6 through 9 of gestation. No significant differences were found between controls and experimental groups in mean implants/female, mean viable fetuses/litter, mean resorptions/litter, frequency of resorptions, frequency of soft tissue anomolies and frequency of skeletal anomalies. Mean fetal weight was significantly heavier in the 0.2 and 0.4 ml/kg groups. This effect is difficult to explain

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20. Abstract Continued

when the 0.6 and 0.8 ml/kg groups showed no increase in fetal weight.

INTRODUCTION

In a variety of occupations there is a risk of exposure to hazardous chemicals. As more women now work in jobs traditionally held by men there is the additional risk that birth defects may result from the exposure of pregnant women. The highest risk of producing birth defects would be in the early stages of gestation when most women would still be working.

It is very difficult to predict the teratogenicity of a chemical based on its structure and there is a low correlation between those substances that are mutagenic and teratogenic (Schardein, 1976). As a result whole animal testing is considered to be the best method for determining teratogenicity and more than one species is necessary because no one species is an adequate indicator for all chemical substances.

The fuel JP-10 is the exoisomer of 4,7-methano-1H-indene, octahydro 12aα, 4α, 7α, 7aα (CA#2825-83-4). It is a specially synthesized fuel used in the Cruise Missile.

Keller, et al. (1981) have examined the effects of JP-10 in Fisher 344 rats. They found tremors and a reduction of maternal weight gain but no differences in fetal weights, resorptions and the incidence of malformations.

This is a report on the teratogenic effects of JP-10 on a second species, ICR mice.

METHODS AND MATERIALS

Sexually mature ICR mice were obtained from Harlan Industries. They were housed in plastic cages on wood chip bedding and received Purina Mouse Chow and water ad libitum. The temperature of the room was maintained at 70-76^{o}F with a 12 hour light cycle. Four to five females were kept with each male. The females were checked for the presence of a vaginal plug early in the morning and again late in the afternoon. The day that a vaginal plug was found was designated as day zero of pregnancy and the females were moved to wire bottomed cages. The pregnant mice were weighed daily.

Pregnant mice were assigned to a control group or to one of four experimental groups. The control group received soybean or mineral oil. The experimental groups received JP-10 diluted with soybean or mineral oil at doses of 0.2, 0.4, 0.6 and 0.8 ml/kg body weight. The substances were given by stomach tube on days 6, 7, 8 and 9 of gestation.

On day 17 of gestation the pregnant females were killed and the fetuses removed by cesarian section. Using the methods from Olson and Back (1978) and Wilson and Warkany (1965), the number and position of each fetus was recorded, weighed and examined for abnormalities. Two thirds of the fetuses were preserved in Bouin's solution, sectioned with a razor blade and examined for soft tissue anomalies. One third of the fetuses were preserved in absolute ethanol, eviscerated, cleared in potassium hydroxide, stained with Alizarin Red S and examined for skeletal anomalies.

The Students T test was used to test for statistical significance between mean values and the Fisher exact test was used to test for significant differences in frequency of resorption and skeletal and soft tissue abnormalities using the litter as the experimental unit.

RESULTS

The following comparisons were made between the control and experimental groups: mean implants/female, mean viable fetuses/litter, mean resorptions/litter, frequency of resorptions, frequency of soft tissue anomaly, and frequency of skeletal anomaly. In all of the above no significant differences ($p = 0.05$) were found between the controls and experimental groups. The data for groups with soybean oil as the vehicle are presented in Tables 1-3.

Table 1.

Effect of JP-10 on the Mean Number of Implantations, Viable Fetuses and Resorptions.

	Control	JP-10			
	Soybean oil	0.2ml/kg	0.4ml/kg	0.6ml/kg	0.8ml/kg
Number of Litters Examined	9	9	9	9	11
Implants/Female Mean ± SE	9.89±1.09	9.89±1.03	9.56±0.73	9.11±1.47	11.82±0.63
Viable Fetuses/litter Mean ± SE	9.0 ±1.25	8.56±1.12	8.78±0.89	9.0 ±1.55	11.27±0.63
Resorptions/litter Mean ± SE	0.78±0.36	1.33±0.41	0.78±0.27	0.11±0.11	0.55±0.27
Number of litters with resorptions	2	6	5	1	4

Table 2.

Effect of JP-10 on the Frequency of Soft Tissue Anomalies

	Control Soybean oil	JP-10 0.2ml/kg	0.4ml/kg	0.6ml/kg	0.8ml/kg
Number of litters (fetuses) examined	9(59)	9(56)	9(54)	9(57)	11(88)
Gastroschisis	1(1)	0	0	0	1(1)
Exencephaly	0	0	0	0	1(1)
Hydronephrosis	0	0	0	0	1(1)
Total litters with anomalies	1	0	0	0	3
% Litters with anomalies	11	0	0	0	27

Table 3.

Effect of JP-10 on the Frequency of Skeletal Anomalies

	Control Soybean oil	JP-10 0.2ml/kg	0.4ml/kg	0.6ml/kg	0.8 ml/kg
Number of litters (fetuses) examined	9(23)	9(21)	9(25)	9(24)	11(36)
Supernumerary ribs	4(4)	5(7)	4(6)	3(4)	3(6)
Total litters with anomalies	4	5	4	3	3
% litters with anomalies	44	56	44	33	27

There was a difference found in mean fetal weights. At doses of 0.2 and 0.4 ml/kg the mean fetal weight was significantly heavier (p=0.05) than in the controls and there was a corresponding higher mean weight gain in the females in these treatment groups and in the 0.8 ml/kg group (Table 4).

Table 4.

Effects of JP-10 on Fetal Weight and Maternal Weight Gain

	Control Soybean Oil	0.2 ml/kg	0.4 ml/kg	0.6 ml/kg	0.8 ml/kg
Number of fetuses	82	77	79	81	124
Mean fetal weight ± S.E.	0.92 ± 0.02	0.99* ± 0.02	1.00* ± 0.01	0.95 ± 0.02	0.95 ± 0.01
Number of females	8	9	9	9	11
Mean maternal weight gain ± S.E.	11.52 ± 1.20	16.66* ± 1.52	17.93* ± 1.55	17.02 ± 2.63	19.21* ± 1.15

* Significant difference from control (p=0.05)

Another series was performed dissolving the JP-10 in mineral oil. The number of litters examined was control, 5; 0.2 ml/kg, 6; 0.4 ml/kg, 9; and 0.6 ml/kg, 10. The results were identical to those found with soybean oil.

DISCUSSION

In ICR mice JP-10 does not cause an increase in fetal malformations. The same result was found by Keller, et al. (1981), after exposing Fisher 344 rats to oral doses of 250, 500 and 1000 mg/kg and an inhalation dose of 572 ppm for six hours per day. All groups were exposed on day 6 through 15 of gestation. They did find that rats receiving 1000 mg/kg and the inhalation dose showed tremors and moderate convulsions and a reduction in maternal weight gain. These effects were not observed in mice.

Mice are more sensitive to the toxic effects of JP-10 having a LD_{50} of 3.9 ml/kg while the LD_{50} in rats is over 20 ml/kg (Kinkead 1979). The concentrations used in the mouse study were higher in proportion to the toxic dose than those in the rat study. Even so there was no increase in the incidence of fetal malformations.

The increased fetal weight in the mouse study is not easily explained particularly when no such increase occurred in the groups receiving 0.6 and 0.8 ml/kg. The increased maternal weight in the 0.2 and 0.4 ml/kg groups is apparently due to increased fetal weight and the increased maternal weight gain in the 0.8 ml/kg group is due to slightly larger average litter size.

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